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Beta-Blocker Heart Attack Trial Study Protocol

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service National Institutes of Health

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Beta-Blocker Heart Attack Trial Study Protocol

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BETA-BLOCKER HEART ATTACK TRIAL (BHAT)

STUDY PROTOCOL

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I. INTRODUCTORY SUMMARY

This protocol describes the essential aspects of the Beta-Blocker Heart Attack Trial (BHAT), a collaborative clinical trial of propranolol in patients with recent myocardial infarction. This trial, comparing propranolol with placebo through a randomized, double-blind design, involves the participation of 31 clinical centers, recruiting approximately 4,200 patients over a period of about 2 years. All patients will be followed to a common termination date 2 years after the last patient has been enrolled. The primary endpoint is death from any cause. Secondary endpoints include fatal and non-fatal coronary events. Toxicity and side effects of propranolol will also be studied, as will possible mechanisms of action. The natural history of myocardial infarction among survivors of recent episodes will be described.

General policies in regard to design, conduct, organization and administration of the BHAT are presented in this protocol. Sample size estimation, definitions, eligibility and exclusion criteria, guidelines for obtaining informed consent, and a listing of participating institutions and investigators are included as appendices.

A Manual of Procedures (MOP) specifies the operations and procedures needed for implementation and execution of the trial.

II. BACKGROUND

Coronary heart disease (CHD) and its complications account for over 600,000 deaths in the U.S. each year. Survivors of a documented myocardial infarction are recognized as having a high risk of dying relative to the general population. Theoretically, an agent which (1) can block the sympathetic nervous activity thought to be involved in precipitating sudden death and (2) has nonneurogenic antiarrhythmic properties, would be of value to people with coronary heart disease. Propranolol, like other beta-blocking agents, has these as well as other properties. It therefore, might be expected to prevent or retard complications of coronary heart disease such as serious arrhythmias. This would be reflected in a decrease in mortality due to coronary heart disease.

The potential long-term value of beta-blocking agents in survivors after an acute myocardial infarction (AMI) had been reported in five controlled clinical trials before the initiation of BHAT. In 1972 Reynolds and Whitlock (British Heart Journal, 34:252-259, 1972) reported on a double-blind study of alprenolol in 78 AMI patients who were followed for 1 year. The major limitation of this study was its small size. The results from two other trials of alprenolol were published in 1974. One by Wilhelmsson et al. (Lancet, ii: 1157-1160, 1974 and Acta Med. Scand., Suppl 575:1-56, 1975) involving 230 AMI-patients was a placebo-controlled double-blind trial with 2 wo years of follow-up. No statistically significant difference between the groups with regard to total mortality was demonstrated. The 7 deaths in the alprenolol group versus 14 in the placebo group were, however, suggestive of a beneficial effect. There

was a marginally significant reduction of sudden death in the alprenolol group. The other alprenolol study, reported by Ahlmark et al. (Lancet, ii:1563, 1974 and Europ J. Clin. Pharmacol, 10:77-83, 1976) was a non-blinded trial involving 162 AMI patients. The findings were similar to those in the Wilhelmsson study. However, an unusual experimental design and high rate of withdrawals limited the value of this study.

The results from two double-blind trials of practolol were published in 1975. Barber et al. (Acta Med. Scand, Suppl 587:213-219, 1975) studied 298 AMI-patients who were followed for 2 years. There was no statistically significant difference in total mortality between the two groups (41 deaths in the practolol group vs. 46 in the placebo group). The Multicentre International Study (British Medical Journal, 3:735-740, 1975 and British Medical Journal, 2:419-421, 1977) involved a total of 3,038 patients treated for up to 3 years (average follow-up was about 14 months) in 67 clinical centers. There were 94 deaths in the practolol group and 117 in the placebo group, a difference of 20 percent. While this difference was not statistically significant, it was suggestive of a beneficial effect of practolol. Subset analyses suggested that the beneficial effect of the drug occurred in patients with anterior myocardial infarctions at entry and that sudden death was reduced more than death from all causes. The main weakness of this trial, which was terminated prematurely because of adverse reactions attributed to practolol, was a high withdrawal rate among high risk patients.

These trials, which demonstrated feasibility and possible efficacy of beta-blocking agents, led the National Heart, Lung, and Blood Institute to sponsor a double-blind, controlled study of propranolol in patients with acute myocardial infarction.

III. OBJECTIVES

The goals of the Beta-Blocker Heart Attack Trial are stated both as primary and secondary objectives to be addressed through analysis of the experience of the total study population, and as subgroup hypotheses to be tested by comparison of outcomes in particular strata within the study population:

A. Primary

The primary objective of this trial is to determine whether or not the regular chronic administration of propranolol to patients who have had at least one documented myocardial infarction will result in a significant reduction in mortality from any cause over the follow-up period. To this end, a total of about 4,200 eligible volunteer patients will be recruited to participate in a double-blind clinical trial within 21 days of the onset of hospitalization for the acute event. One-half of the patients will be randomly assigned to propranolol and one-half to placebo.

B. The secondary objectives are to evaluate:

1. The effect of chronic administration of propranolol to persons with documented myocardial infarction on:

   a) Incidence of coronary heart disease mortality.

   b) Incidence of sudden cardiac death, defined as death within 1 hour of onset of symptoms.

   c) Combined incidence of nonfatal myocardial infarction plus coronary heart disease mortality.

2. Possible adverse effects of propranolol in chronic use.

3. Possible mechanisms of action of propranolol if it is successful in reducing mortality or morbidity.

4. The natural history of coronary heart disease in the placebo group population.

C. In addition, the following subgroup hypotheses will be tested:

1. Propranolol is effective in reducing mortality due to sudden cardiac death in patients with prior myocardial infarction who have complex premature ventricular contractions* (PVC's) at baseline. (Complex premature ventricular contractions are defined as runs of 2 or more PVC's, multiform PVC's, and more than 10 PVC's per hour.)

2. Propranolol is effective in reducing mortality due to sudden cardiac death in patients with prior anterior acute myocardial infarctions.

IV. DESIGN

A. Introduction

The target population for the BHAT includes men and women aged 30 through 69 years admitted to hospital coronary care units (CCUs) or their equivalent and having a confirmed acute myocardial infarction on the current admission. Patients who have contraindications to use of propranolol, conditions where prescription of propranolol by private physicians is judged highly likely, or other conditions felt likely to impair long-term participation will not be eligible for the BHAT.

After completion of the baseline reference examination the eligible patients will be randomized and drug regimen initiated.

*Based on analysis of 24 hours of recorded ECG by a semiautomated method.

READEX

Length of follow-up for each patient will depend on the date of entry to the study, since all patients will be followed to a common termination date. Given about 2 years for recruitment of patients, patient follow-up will range from 2 to 4 years.

Specifications of the estimation of sample size for the BHAT are presented in Appendix A. In general, the estimate that a total of 4,200 patients must be recruited rests on several assumptions: the age, sex and clinical status of eligible patients; immediacy of effect of the drug; dropout of patients on propranolol and drop-in of patients on placebo; an average of 3 years of follow-up; total mortality as the primary endpoint; and a two-tailed significance level (α) of 0.05 and power ($1-\beta$) of 0.90. To permit recruitment of patients within a desirable interval of time, 31 clinical centers will participate with a projected average enrollment of approximately 135 patients randomized and followed by each center.

B. Recruitment and Enrollment

1. Eligibility Assessment

a. BHAT Log

To assist in the recruitment, a log of all patients admitted to the cooperating CCU's will be kept during the recruitment phase. The log will provide a tool to monitor recruitment at each center, will help to ensure that every CCU admission receives consideration for enrollment into the BHAT, and will assist in developing comparisons of yield from each CCU and clinical center.

b. Eligibility

During the first few days after a patient's admission to a CCU, the patient's eligibility for the study will be evaluated. Clinical history, electrocardiographic changes, and serum enzymes will be used to determine this eligibility. Patients eligible for this study are men and women, age 30 through 69 years, with one or more documented myocardial infarctions. Patients will be recruited while in the hospital for an acute myocardial infarction and enrolled into the study before discharge. Eligible patients must fulfill the study definition of an acute myocardial infarction. The diagnosis will be based either on electrocardiographic records showing evolving Q or QS changes and ST segment and T wave

changes or elevated serum enzymes and appropriate clinical history together with specified ECG criteria (Appendix B). Electrocardiograms from the qualifying myocardial infarction will be subsequently read by the ECG Center.

c. Exclusions

Otherwise eligible patients are to be excluded from enrollment if any of the following types of conditions apply (a listing of these excluding conditions is given in Appendix C):

1) relative or absolute contraindications to the administration of propranolol;

2) medical conditions for which propranolol is a highly probable treatment drug of choice;

3) presence of any disease other than the patient's CHD associated with a reduced likelihood of survival for the duration of the trial;

4) reasons relative to study design;

5) the qualifying myocardial infarction resulted from a probable nonatherosclerotic cause;

6) adherence to the study protocol is likely to prove especially difficult.

d. Informed Consent

After the patient's clinical status has stabilized, the study with its possible benefits and risks will be discussed with the patient's physician and with the patient. A brochure containing such information is available. Prior to the baseline reference examination the patient will be asked to sign a consent form.

2. Baseline Reference Examination and Ambulatory ECG Monitoring

After the patient has been given a detailed explanation of the trial and has signed an Informed Consent Form and is free of exclusion criteria, the baseline reference examination should be performed. This examination must occur prior to discharge from the hospital, but not later than 21 days following admission to the CCU.

The primary purpose of the baseline reference examination is to establish baseline values of study variables.

The baseline reference examination includes a clinical history, a physical examination, an electrocardiogram, a PA chest X-ray, urinalysis, hematocrit, white blood cell count, serum cholesterol, serum potassium, SGOT, and serum creatinine.

A 24-hour ambulatory ECG monitoring should be obtained on all patients at baseline. A 1-hour segment will be analyzed in all patients with the full tape analyzed in a randomly chosen subset of 1,000 patients. The possibility exists for 24 hour analysis on additional patients.* After the baseline reference examination has been done, a standard baseline form will be completed.

3. Randomization

Randomization of patients to either propranolol or placebo will take place immediately after completion of the baseline reference examination.

The random assignment to one of the two study groups will be made by the Coordinating Center and transmitted to the clinical center by telephone (hard copy to follow) after verification that the steps mentioned above have been completed. Each patient will be assigned an identification number which has a drug code incorporated in it. Upon completion of these steps each patient will be counted as a member of the original treatment group to which he or she was assigned, regardless of subsequent adherence or clinic attendance. For the purpose of analysis no patients will be withdrawn from the trial and every effort will be made to ascertain the occurrence or nonoccurrence of the primary endpoint.

Included in the randomization scheme will be:

a) stratification by clinical center.

b) blocking within each clinical center.

C. Treatment Protocol

1. Dosage Schedule

Immediately after randomization (Day 0), all patients will be given a 20 mg tablet of appropriate PHAT medication. After administration of this first dose, the

*Subsequently, it was decided to perform 24-hour analysis on all baseline tapes.

patients will be closely observed for occurrence of adverse reactions. If no adverse reactions are noted and if the 1st dose of 20 mg is administered early enough in the day, a second dose of 20 mg may be administered on day 0, 8 hours after the first dose.

Again, if no adverse reactions are noted, the dose should be increased to 40 mg every 8 hours not earlier than Day 1 (the day following randomization) and as soon thereafter as possible, but no later than Day 7. No earlier than the third day of the 40 mg every 8 hours schedule, but no later than Day 10, and 8 hours after the most recent dose, blood will be drawn for a serum propranolol determination.

Just prior to discharge the patient will be given a supply of study medication and instructed as to frequency and dose of the drug. The patient will also be advised against taking nonstudy propranolol (propranolol not provided by BHAT) or other beta-blockers and warned against stopping the study medication in a precipitous manner.

The patient will be continued on a schedule of 40 mg three times a day until the 1-month visit. At that time, if there are no contraindications, his or her dose will be increased to 60 or 80 mg three times a day, depending on the serum propranolol level obtained 3 to 10 days after randomization. If it is below 20 nanograms per milliliter, the Coordinating Center will so notify the clinical center. In the absence of contraindications, these patients' dosage will be raised to 80 mg three times a day at the 1-month visit, rather than to 60 mg three times a day. The Coordinating Center will also notify the clinical centers about patients on placebo concerning increasing the dose to 80 mg three times a day in order to maintain the blinded nature of the study. If a patient is scheduled to be raised to 80 mg three times a day, but this cannot be done at the 1-month visit, it may be done at any subsequent time during the study. As always, the clinical center physician is responsible for ensuring that these changes are consistent with the well-being of the patient. A patient's study medication may be reduced or stopped at any time if there is evidence of drug toxicity or serious side effects.

2. Serum Propranolol Determinations

Serum propranolol levels will be determined by a high pressure liquid chromatography method at the Central

Laboratory. Blood will be obtained at the following times for this determination:

Three to ten days after randomization.

One and one-half months after randomization.

Six months after randomization and subsequently at semiannual intervals.

Only the determination obtained 3 to 10 days after randomization will be used to adjust dosage level.

3. Adherence Measures

Both serum propranolol levels and pill counts will be used to evaluate patient adherence to study medication. In addition, missed patient visits and patient dropouts will be monitored. These measures will be reviewed by the Adherence Subcommittee in a manner so as not to unblind the treatment. To ensure this all data released will be initially approved by the Policy Data Monitoring Board. Adherence reports will periodically be sent to each clinical center in an effort to keep patient adherence at a high level.

Similar reports, with data reported by treatment group, will be sent to the Policy Data Monitoring Board for review.

D. Follow-up Schedule

The purposes of the 1-month post-randomization visit are to assess overall health status, adherence, and possible side effects or toxicity of the treatment regimen, and to increase drug dosage.

At 1½ months post-randomization all patients will return for reassessment of status, for drawing a second serum propranolol specimen, and for obtaining 24-hour ambulatory ECG monitoring on the randomly chosen subset of 1,000 patients who were initially identified at baseline as scheduled to have the full 24-hour baseline tape analyzed.

Thereafter, all scheduled follow-up visits will occur at 3-month intervals dated from the time of randomization. The purposes of these visits are to monitor the experience of the two treatment groups in parallel and to reinforce continuing participation in the trial.

Those visits which occur at 12, 24, 36 or 48 months after randomization will be designated as annual visits. On these occasions the regular three monthly evaluation will be supplemented with additional procedures, as outlined below.

At each visit, monitoring of adherence, toxicity and side effects, health status, use of nonstudy medication, and interval illnesses, operations and possible endpoints will be carried out and recorded on standardized study forms for entry in each patient's central data file. Laboratory and special examination procedures will be obtained as summarized in Table 1.

The annual laboratory tests performed in BHAT are not meant to detect possible drug toxicity in individual patients. Rather, they will indicate if group differences are present. As a consequence, they cannot supplant usual good clinical care of the patient. Of course, if extreme laboratory values are noted, the clinical center physician will be immediately notified, rather than through the usual reporting mechanisms.

The patient will remain in the care of his or her private physician for all medical matters unrelated to the study.

E. Mortality Follow-up

Ascertainment of death of patients in the BHAT will be carried out by each local center. The vital status of all participants who fail to attend scheduled visits will be determined. Deaths will be reported immediately to the Coordinating Center even if supporting documents are not yet available.

Documentation of the cause of death of a patient will be based on information from witnesses, relatives, death certificate, autopsy report when available and hospital records.

A Mortality Classification Subcommittee will be established whose responsibilities will include independent review of information on all deaths by at least two members. Classification of cause and circumstances surrounding death will occur upon agreement between the reviewers (either initially or after an adjudication session).

V. CONDUCT OF THE TRIAL

A. Time Schedule

Planning and Organization of Study	September, 1977 through May, 1978

Table 1. BHAT Procedures

Visit	Holter*	ECG*	Chest** X-ray	Propranolol*	Hematocrit*** WBCC Urinalysis	Potassium*	Cholesterol* SGOT Creatinine
Baseline	X	X	X	X+	X	X	X
1½ mo.	X(Subset)			X		X	
6 mo.				X			
12 mo.		X	X	X	X	X	X
18 mo.				X			
24 mo.		X		X	X	X	X
30 mo.				X			
36 mo.		X		X	X	X	X
42 mo.				X			
48 mo.		X		X	X	X	X

* Analyzed centrally.

** Chest X-ray will be analyzed at local clinical center. A third X-ray will be obtained at the time of the final study visit.

*** Analyzed at local clinical center.

\+ Done 3 to 10 days after baseline.

Review of Study Protocol by Policy Data Monitoring Board	February, 1978
Recruitment and Training of Staff	March, 1978 through May, 1978
Recruitment of Patients	June, 1978 through Fall, 1980
Follow-up Period	Fall, 1980 through Summer, 1982
Phase-Out of Study	Summer, 1982 through Fall, 1982
Data Analysis	Summer, 1982 through December, 1983

B. Training and Orientation

During April 1978, regional training and orientation sessions took place. Personnel from the Project Office, the Coordinating Center, the ECG Center and the Central Laboratory trained appropriate clinical center personnel in the use of the Manual of Procedures. This training included the correct procedures for completion of all study forms, recording of ECG's and Holter monitoring, and collection and shipment of serum to the Central Laboratory. Also included in these sessions was detailed instruction for communicating with the Coordinating Center regarding the determination of eligibility and the assignment of patient identification numbers. After training and orientation sessions were completed, the Manual of Procedures and study forms were pretested.

C. Protection of Human Subjects

1. Patient Safety

At each clinical center, the standard interval history and physical examination will elicit information concerning toxic reactions and side effects in BHAT patients. As always, the clinical centers physician is responsible for ensuring that the prescribed dosage of the study medication is consistent with the well-being of the patient. The Central Laboratory will notify the clinical center immediately regarding chemistry values requiring special attention. If a situation arises where it is in the best interest of the patient that the study drug be identified, this information will be available through the local clinical center pharmacy or from the Coordinating Center.

The following indications for stopping or reducing study medication are for the safety of the patient and for the integrity of the study:

a) A patient must be taken off study medication if he or she is placed on nonstudy propranolol or any other beta-blocking agent. Study medication is to be resumed when these drugs are discontinued.

b) Temporary drug withdrawal should be considered during procedures likely to lead to unblinding.

c) Withdrawal of study medication due to possible drug toxicity or any other circumstance in which propranolol may be contraindicated will occur at the discretion of the clinical center physician. If cessation or reduction of study medication is indicated, the following schedules are recommended:

   i) In an emergency, treatment may be stopped rapidly, as long as the patient is carefully monitored in the hospital, by approximately halving successive doses at 8 hour intervals.

   ii) If no emergency exists, several days may be taken to stop or reduce study medication by approximately halving the daily dose every 48 hours.

   Of course, any schedule intermediate between the emergency ones and the nonemergency ones may be used where appropriate.

A Policy Data Monitoring Board, the members of which do not participate in BHAT as investigators, will periodically evaluate both adverse and beneficial drug effects. This will enable the study to be terminated earlier than planned if the data warrant and will help ensure the safety of the patients.

2. Confidentiality

All correspondence will refer to patients by numerical code only. Information transmitted to the Coordinating Center on BHAT patients will be held in strict confidence and stored in locked files or filing rooms. Information stored on disk and/or tape files for automatic data

processing will not be identifiable by any personal items. All statistical reports generated will contain no identification of individual patients.

3. Informed Consent

For detailed guidelines on obtaining informed consent see Appendix D.

D. Data Monitoring and Quality Control

Study data will be monitored closely by the Coordinating Center. Frequent reports will be generated on form completion and error rates for each clinical center. An automatic forms accounting and monitoring system will be initiated for each participant at the time of randomization. This system provides the capability to monitor the status, volume, and disposition of study forms as well as identify forms due, overdue, and backlogged. In addition all study forms will undergo an extensive computer edit which provides information to the clinical centers on quality control to help improve and maintain data quality. Both the Central Laboratory and the ECG Center carry out quality control procedures designed to detect inaccuracies and inconsistencies. This information will be used in making decisions to adjustment procedures, re-analyze blood specimens or rereading electrocardiograms. These quality control data will be made available to the Quality Control Subcommittee.

All randomized patients will remain in their originally assigned groups for purposes of analysis, regardless of subsequent central determination of eligibility. During the recruitment period, the Coordinating Center will determine eligibility of subjects and will provide ongoing reports to the clinical centers regarding inappropriately enrolled patients. This will minimize the enrollment of additional ineligible patients.

To provide independent evidence of the consistency of the blood analyses and ECG interpretation, external blind surveillance procedures will be carried out. Test blood samples, test ECG tracings and test ambulatory ECG monitoring tapes will be processed in a manner similar to regular study materials so that the performance of the entire system may be monitored.

E. Data Analysis

The primary statistical analyses of the mortality and morbidity results of the BHAT will be carried out using life table methods. This allows one to observe the pattern of mortality

and morbidity by treatment group and can take into account varying lengths of follow-up. Statistical tests of the difference in mortality from any cause, mortality from coronary heart disease, sudden cardiac death, and combined nonfatal myocardial infarction plus coronary heart disease mortality between the two treatment groups will be computed throughout the study and at the end of the follow-up period. These data will be monitored and submitted to the Policy Data Monitoring Board on a regular basis during the study, to permit early termination of the study should the data warrant.

Other analyses of interest will be done in an attempt to identify subgroups where propranolol is particularly beneficial. All subgroup analyses will employ baseline characteristics.

VI. ORGANIZATIONAL STRUCTURE

A. Introduction

The participating units in this collaborative clinical trial currently include the following: thirty-one individual clinical centers, a Coordinating Center, an ECG Reading Center, a One-Hour Ambulatory ECG Reading Center, a 24-hour Ambulatory ECG Reading Center, a Central Laboratory, the NHLBI Project Office, and a Drug Distribution Center. The units in the study are tied together through a study administration, which will maintain operations in the study and ensure effective communication and cooperation among the various study units. During the Planning Phase, a Planning Committee represented the various investigators. Currently, the administrative units include a Policy Data Monitoring Board, a Steering Committee, various Subcommittees and an Assembly of Investigators.

B. Participating Units

The functions of the participating units of the Beta-Blocker Heart Attack Trial are described below.

1. Clinical Centers

Thirty-one clinical centers are responsible for recruiting the required number of patients, administering the study drugs, coordinating patient care, and collecting the information required by the study protocol. The principal investigator is responsible for the overall conduct and performance of the clinical center. The professional and clerical organization of each clinical center will differ, but each clinical center has one

person specifically identified as the clinic coordinator. This person will be responsible for such critical matters as checking coronary care unit logs, maintaining good patient adherence, appointment scheduling, and checking the completeness of forms. He or she will also monitor shipment of blood specimens to the Central Laboratory and collection of scheduled and interim event ECG's.

2. Coordinating Center

The Coordinating Center has a major role in the design, implementation, and execution of the study. The staff have the responsibility for collecting, editing, analyzing, and storing all data received from the clinical centers, Central Laboratory and the ECG Reading Centers. Some specific functions of the Coordinating Center are to work with the investigators in the development and pretesting of forms and procedures and in the preparation of the Manual of Procedures, to make a random assignment to a treatment group for each patient, to assume responsibility for review of all data transmitted on study forms, to check the completeness of records and periodically prepare performance reports to participating clinical centers, to analyze periodically the frequency of new events and toxic side reactions by treatment group and to report these data to the Policy Data Monitoring Board, to prepare interim technical and statistical reports for the periodic meetings of the Assembly of Investigators, to prepare recruitment charts for each clinical center, and to assist in the preparation of reports of the study for publications.

3. ECG Reading Centers

The ECG Reading Center will read and code all of the standard ECG's collected at baseline and at follow-up (qualifying, baseline, annual and interim event). The Center is responsible for developing diagnostic criteria for qualifying and recurrent myocardial infarction. The Center will also periodically review the performance of the clinical center ECG technicians and the quality of clinical center ECG machines.

The One-Hour Ambulatory ECG Reading Center is responsible for evaluating quality control of the ambulatory ECG recordings and for reading and coding 1 hour segments from each of the 4,200 baseline ambulatory ECG's and 1,000 6-week follow-up ambulatory ECG's. The 24-Hour Ambulatory ECG Reading Center is responsible for reading and coding

the full 24 hours on 1,000 randomly selected baseline recordings* and the 1,000 6-week follow-up recordings.

4. Central Laboratory

The Central Laboratory will perform selected laboratory tests for all patients enrolled in the study. These will include serum determination of cholesterol and potassium, of drug adherence tests (serum propranolol) and tests for potential drug toxicity (SGOT, and creatinine). The results of all laboratory tests will be forwarded to the Coordinating Center and certain tests will also be reported routinely to the clinical centers. In cases of abnormal results which may indicate drug toxicity, the Central Laboratory will notify the clinical center as soon as possible so that appropriate action may be taken.

5. National Heart, Lung, and Blood Institute Project Office

The National Heart, Lung, and Blood Institute is responsible for providing organizational, scientific, and statistical direction to the study through the Clinical Trials Branch, Division of Heart and Vascular Diseases. The Scientific Project Officer is a voting member of the Steering Committee as well as a nonvoting member of the Policy Data Monitoring Board. Other NHLBI staff will also participate in cooperation with the individual clinical centers, Coordinating Center, Central Laboratory, ECG Reading Centers and Drug Distribution Center.

The Contract Officer is responsible for all administrative matters related to award and conduct of contracts.

6. Drug Procurement and Distribution Center

The U.S. Public Health Service Supply Service Center at Perry Point, Maryland, will serve as a central procurement, storage and distribution point for the study medications.

C. Study Administration

1. Planning Committee

During the Planning Phase of the study, the Planning Committee had responsibility for developing the final study protocol and for initiating the development of the Manual of Procedures and study forms.

*Subsequently modified to including reading of all baseline recordings.

The Planning Committee was composed of principal investigators of the clinical centers, the Coordinating Center, the ECG Reading Center, the Central Laboratory, and the staff of the NHLBI Project Office. This committee was dissolved upon the establishment of the Steering Committee and Assembly of Investigators.

The following subcommittes of the Planning Committee were established:

a. Design Subcommittee

This subcommittee looked at issues such as double versus single blind, stratification, subgroup hypotheses, baseline schedule, and follow-up visit schedule.

b. Eligibility Subcommittee

This subcommittee defined patient exclusion criteria, qualifying myocardial infarction criteria, developed a common coronary care unit log; and worked on informed consent.

c. Pharmacology and Bibliography Subcommittee

This subcommittee recommended study drug dosage schedule, suggested laboratory tests for monitoring adherence and toxicity, and began a literature search on propranolol.

d. Arrhythmia Monitoring Subcommittee

This subcommittee recommended procedures for arrhythmia monitoring, using ambulatory ECG equipment, at baseline and follow-up.

e. Endpoints Subcommittee

This subcommittee defined fatal and nonfatal events and endpoints to be measured during the study and specified appropriate ways of evaluating these events.

f. Standardization Subcommittee

This subcommittee suggested appropriate internal and external monitoring of the clinical centers and central units and developed training sessions for center personnel.

g. Recruitment and Special Studies Subcommittee

This subcommittee established guidelines for patient recruitment, and prepared a patient recruitment brochure. During the Planning Phase, it reviewed ancillary study proposals and suggested special studies which might be performed by one or more clinical centers.

2. Steering Committee

Subsequent to the Planning Phase, the Steering Committee provides scientific direction for the study at the operational level. The permanent members of the Steering Committee are the chairman and two other appointed clinical center investigators, the principal investigators of the Coordinating Center, Central Laboratory, ECG Reading Centers and the NHLBI Project Officer. There are, in addition, six or seven members who are principal or co-principal investigators of the participating clinical centers. These representatives will be assigned for 1-year terms. In this way, all centers will have had representation on the Steering Committee by the end of the trial.

Specific functions of the Steering Committee will be:

a. To provide overall scientific direction for the study at the operational level.

b. To advise and assist the Coordinating Center, Central Laboratory, ECG Reading Centers and Drug Distribution Center on operational matters.

c. To monitor the performance of the individual clinical centers with regard to patient recruitment and adherence to study medication.

d. To monitor the quality of the performance of the clinical centers and the central units.

e. To review all proposed ancillary studies.

f. To keep the Assembly of Investigators informed about the progress of the trial.

g. To report major problems to the Policy Data Monitoring Board.

h. To make recommendations concerning changes in the Protocol to the Policy Data Monitoring Board.

The Steering Committee will meet semiannually in conjunction with meetings of the Assembly of Investigators. Additional meetings of the Steering Committee will be called by its chairman as necessary.

In cases where urgent decisions are required, the officers of the study, the chairman of the Steering Committee, the Project Officer, and the Coordinating Center principal investigator, will be empowered to make such decisions and then report them to the Steering Committee and Assembly of Investigators.

3. Assembly of Investigators

The Assembly of Investigators will represent all of the operations units participating in the study. The principal investigator or one coinvestigator from each clinical center, and one representative each from the Coordinating Center, the Central Laboratory, the NHLBI Project Office, and the ECG Reading Centers (resting and ambulatory) will be voting members of the Assembly of Investigators. Other personnel from the clinical centers, Coordinating Center, Central Laboratory, ECG Reading Centers, and NHLBI will attend Assembly of Investigator meetings as nonvoting members.

The Assembly of Investigators will meet semiannually to review the progress of the study and to vote on major issues.

4. Subcommittees

The following subcommittees are appointed:

a. Adherence Subcommittee:

This subcommittee will monitor patient adherence and will review methods for maintaining good adherence to study treatment protocol and medication.

b. Bibliography Subcommittee:

This subcommittee will create and maintain a current bibliography on propranolol and other beta blocking agents pertinent to BHAT. It will also review appropriate published material at the semiannual meetings.

c. Editorial Review Subcommittee:

This subcommittee will review and recommend approval or disapproval of every scientific paper using unpublished BHAT data (including ancillary study data) as well as every paper using published BHAT data that purports to represent official BHAT views or policy. This applies to papers prepared for publication or oral presentation. The subcommittee will also review proposed ancillary studies to ensure that patient safety and BHAT design and scientific integrity are not compromised. In addition, it will suggest special studies which might be conducted at one or several clinical centers on an ancillary basis.

d. Holter Monitoring Advisory Subcommittee:

This subcommittee will advise the Ambulatory ECG Center(s) and the Steering Committee on questions relating to methodology and analysis of Holter recordings. Outside experts may be added to this subcommittee on an ad hoc basis.

e. Mortality Classification Subcommittee:

This subcommittee will review all information concerning cause and circumstance of death of BHAT patients and will code this information for each decedent.

f. Natural History Subcommittee:

This subcommittee will suggest appropriate natural history analyses based on placebo group data. It will initiate publications and presentations based on these analyses.

g. Nonfatal Events Subcommittee:

This subcommittee will classify, in a blind, standardized fashion, specified nonfatal events. Its primary function will be to review and classify information concerning nonfatal myocardial infarctions.

h. Quality Control Subcommittee:

This subcommittee will monitor the performance of the clinical centers and the central units. Blinded data will not be reviewed by this subcommittee.

5. Policy Data Monitoring Board

The Policy Data Monitoring Board acts in a senior advisory capacity to the NHLBI on policy matters throughout the duration of the study. In addition, it periodically reviews study results by treatment group and evaluates the study treatment for beneficial and adverse effects.

The Board will consist of a chairman, six additional voting members who are appointed by the NHLBI for the duration of the study and the NHLBI Project Officer as an exofficio, nonvoting member. Board meetings will be attended by senior representatives from the Coordinating Center and NHLBI, as well as the chairman of the Steering Committee, and when appropriate, by representatives from the Central Laboratory and ECG Reading Centers. Additional Board members may be appointed if deemed necessary by the NHLBI in response to recommendations from the Board. No voting member of the Policy Data Monitoring Board may participate in the study as an investigator. Others in his institution, however, will not be excluded from participation because of his Board membership. Meetings of the Board will be called by the chairman at least twice a year.

Specific functions of the Policy Data Monitoring Board are:

a. To initially review the Protocol and make recommendations to the Director of NHLBI.

b. To review subsequent changes in the Protocol and make recommendations to the NHLBI.

c. To examine endpoint and toxicity data by treatment group at least once every 6 months.

d. To make recommendations to the NHLBI on any proposed early termination of the study because of beneficial or adverse drug effects.

e. To assist the NHLBI in resolving problems referred by the BHAT Steering Committee.

f. To review the performance of the individual clinical centers and central units.

g. To make recommendations to the NHLBI on the discontinuation of any centers which perform unsatisfactorily.

SAMPLE SIZE FOR BHAT

The sample size for the Beta Blocker Heart Attack Trial (BHAT) is based on several assumptions. These include:

1. Men and women, ages 30-69, with one or more documented MI who are currently in the hospital for an MI will be recruited over a 2-year period and randomized into one of two groups, propranolol or placebo, before being discharged.

2. The primary endpoint will be total mortality over the follow-up period. All patients will be followed for a minimum of 2 years and possibly up to 4 years, or on the average 3 years, assuming an even recruitment.

3. The 3-year mortality rate in this group based on other studies is estimated to be 18 percent ($p_c = 0.18$). The treatment propranolol is assumed to reduce the total 3-year mortality by 28 percent ($p_e = 0.1296$) based on the European beta-blocker studies.

4. Propranolol's proposed therapeutic effect is immediate.

5. The significance level, 2α, is 0.05 with the hypothesis being two-sided; i.e. H_0: $p_c = p_e$ vs. H_A: $p_c \neq p_e$.

6. The power, the probability of finding a specified difference given that it actually exists, has been set at 0.90.

7. The noncompliance rate in the treatment group, referred to as the "dropout" rate, which is the rate at which those patients who were randomized to propranolol stop their treatment, has been assumed to be 12 percent the first year, 8 percent the second and 6 percent the third for a total of 26 percent total 3-year dropout. The dropout rates are based on other studies including post MI patients.

8. For the control group, the noncompliance rate involves patients randomized to placebo taking propranolol or similar drug and in effect "dropping in" on the treatment regimen. The drop-in rates have been assumed to be 7 percent for each year of the study or a total of 21 percent for the 3 years.

9. Based on a method developed by Halperin et al. (J. Chron. Dis. 21: 13, 1968), the dropout rate adjusts the nominal $p_e = 0.1296$ upward (back toward the p_c rate) to a realized $p_e^* = 0.1375$. This method takes into account the dropout rate. The method of Halperin has been modified to adjust the control rate $p_c = 0.18$ downward due to "drop-ins" towards the nominal treatment rate to obtain a realized control rate of $p_c^* = 0.1746$.

10. Based on the adjusted rates $p_e^* = 0.1746$, $p_e^* = 0.1375$, $2\alpha = 0.05$ and power = 0.90, the total sample size (2N) for this study has been estimated to be approximately 4,020. This was adjusted upwards to 4,200 for administrative purposes.

BHAT DEFINITIONS OF ACUTE MYOCARDIAL INFARCTION

Class I. (The symptom and enzyme changes establish the infarct as acute. Only a single ECG recording is needed for this classification);

1. Presence of Q or QS findings (any Minn. code 1-1-1 through 1-3-6, see definition)

PLUS

2. ST abnormality (Minn. code 9-2--ST elevation 1 mm or more in limb leads or ST elevation 2 mm or more V1-V4) and/or T wave abnormality (Minn. code 5-1 or 5-2 --negative or inverted T wave of at least 1 mm or more.

PLUS

3. Absence of LBBB and WPW

PLUS

4. Typical symptoms of acute myocardial infarction (see definition)

PLUS

5. Elevated serum enzymes (see definition)

Class II. (An evolving pattern of Q or QS changes (appearance or disappearance) establishes the infarct as acute. Two or more ECG recordings from the acute event within 10 days of each other are needed for this classification, which does not require typical history or enzyme elevation);

1a. One ECG record showing no Q code and another record with Q or QS finding (Minn. code 1-1-1 through 1-2-7)

OR

1b. One ECG record showing minor Q code (Minn. code 1-2-8 or 1-3) and another record showing a major Q or QS finding (any Minn. code 1-1)

PLUS

2a. One ECG record showing no ST elevation and another record showing ST elevation (Minn. code 9-2--ST elevation 1 mm or more in limb leads or 2 mm or more in precordial leads V1-V4)

2b. One ECG record showing no T wave inversion and another record showing T wave inversion (Minn. code 5-1 or 5-2--negative) or inverted T wave of at least 1 mm or more.

OR

2c. One ECG record showing no major ST segment depression and another record showing major ST segment depression (Minn. code 4-1--ST-J depression at least 1 mm with ST segment horizontal or downsloping).

PLUS

3. Absence of LBBB or WPW

Class III. (This classification covers subendocardial infarcts and therefore does not require any Q or QS code. The clinical symptom and enzyme changes establish the infarct as acute. Subgroup a) requires only one ECG recording, subgroups b-d require two ECG records):

1. Typical symptoms of acute myocardial infarction (see definition)

PLUS

2. Elevated serum enzymes (see definition)

PLUS

3a. ST elevation (Minn. code 9-2--ST elevation 1 mm or more in limb leads or 2 mm or more V1-V4) and ST depression (Minn. code 4-1 or 4-2--ST-J depression at least 1 mm with ST segment horizontal or downsloping) in the same record.

OR

3b. Increasing or decreasing ST elevation; one record showing no Minn. code 9-2 (ST elevation 1 mm or more in limb leads or 2 mm or more V1-V4) and another record has a Minn. code 9-2. (Compare least and greatest ST elevation.)

OR

3c. Increasing or decreasing ST depression by comparing the least and greatest ST segment abnormalities; one record shows no or minor ST depression (Minn. code 4-3 or 4-4--ST-J depression less than 0.5 mm with downsloping ST segment at least 0.5 mm below PR

baseline or ST-J depression of 1 mm or more with upsloping ST segment) and another record showing a major ST segment depression (Minn. code 4-1 or 4-2--ST-J depression at least 0.5 mm with ST segment horizontal or downsloping).

OR

3d. Increasing or decreasing T waves by comparing the least and greatest T wave inversion; one record shows no or minor T wave inversion (Minn. code 5-3--T amplitude less than 1 mm inverted but not positive) and another record showing T wave inversion (Minn. code 5-1 or 5-2--T amplitude negative or inverted at least 1 mm).

4. Absence of LBBB and WPW.

DEFINITIONS

Elevated Serum Enzymes:

- An elevation of two or more of the enzymes SGOT, total LDH, total CPK and HBD, of at least twice the upper limits of normal in the local laboratory. (Instead of an elevation of CPK of at least twice the upper limits of normal, an elevation of CPK-MB may be used.)

  Occurring within 72 hours of the onset of symptoms of the acute event.

OR

- An elevation of SGOT of at least three times the upper limit of normal in the local laboratory,

- Occurring within 72 hours of the onset of symptoms of the acute event.

Typical Symptoms of Acute Myocardial Infarction

- Severe discomfort occurring anywhere in the anterior chest, back, epigastrium, jaw, neck, shoulder, elbow, forearm or wrist.

- This severe discomfort must be present more than 30 minutes unless relieved by morphine or meperidine.

Minnesota Code for Classification of ECG Changes

Q Wave Codes (myocardial necrosis)

(1) Anterolateral infarction pattern (leads I, aVL, V6)

1-1-1 Q/R amplitude ratio 1/3 or more plus Q duration 0.03 second or more in any of leads I, V6, or QS in lead I or V6.

1-1-2 Q duration 0.04 second or more in any of leads I, V6.

1-1-3 Q duration 0.04 second or more, plus R amplitude of 3 mm or more in lead aVL.

1-2-1 Q/R amplitude ratio 1/3 or more plus Q duration at least 0.02 second and less than 0.03 second in any of leads I, V6.

1-2-2 Q duration at least 0.03 second and less than 0.04 second in any of leads I, V6.

1-3-1 Q/R amplitude ratio at least 1/4 and less than 1/3 plus Q duration of at least 0.02 second and less than 0.03 second in any of leads I, V6.

1-3-3 Q duration of at least 0.03 second and less than 0.04 second, plus R amplitude of 3 mm or more in lead aVL.

(2) Inferior infarction pattern (leads II, III, aVF)

1-1-1 Q/R amplitude ratio 1/3 or more plus Q duration 0.03 second or more in lead II.

1-1-2 Q duration 0.04 second or more in lead II.

1-1-4 Q duration 0.05 second or more in lead III plus any Q wave of at least 1.0 mm amplitude in aVF.

1-1-5 Q duration 0.05 second or more in lead aVF.

1-2-1 Q/R amplitude ratio 1/3 or more, plus Q duration at least 0.02 second and less than 0.03 in lead II.

1-2-2 Q duration at least 0.03 second and less than 0.04 second in lead II.

1-2-3 QS pattern in lead II.

1-2-4 Q duration of at least 0.04 second and less than 0.05 second in lead III, plus any Q wave of at least 1.0 amplitude in aVF.

1-2-5 Q duration at least 0.04 second and less than 0.05 second in lead aVF.

1-2-6 Q amplitude of 5 mm or more in either of leads III, aVF.

1-3-1 Q/R amplitude ratio at least 1/5 and less than 1/3 plus Q duration of at least 0.02 second and less than 0.03 second in lead II.

1-3-4 Q duration of at least 0.03 second and less than 0.04 second in lead III, plus any Q wave at least 1.0 mm amplitude in lead aVF.

1-3-5 Q duration of at least 0.03 second and less than 0.04 second in lead aVF.

1-3-6 QS pattern in each of leads III and aVF.

(3) Anteroseptal and anterior infarction pattern (leads V1, V2, V3, V4, V5)

1-1-1 Q/R amplitude ratio 1/3 or more plus Q duration 0.03 second or more in any of leads V2, 3, 4, 5.

1-1-2 Q duration 0.04 second or more in any of leads V1, 2, 3, 4, 5.

1-1-6 QS pattern in any of leads V2, 3, 4, 5, when an initial R wave is present in any beat in the adjacent lead to the right on the chest. For lead V1 an initial R is considered present when the majority of beats have an initial positive inflection in the QRS of $\geq$1/4 mm in that lead. For leads V2-V5 an initial R wave is considered present in a lead when any initial positive inflection in the QRS measures $\geq$1/4 mm in that lead.

1-1-7 QS pattern in all of leads V1 to V4, or V1 to V5.

1-2-1 Q/R amplitude ratio 1/3 or more, plus Q duration at least 0.02 second and less than 0.03 second in any of leads V2, 3, 4, 5.

1-2-2 Q duration at least 0.03 second and less than 0.04 second in any of leads V2, 3, 4, 5.

1-2-7 QS pattern in all of leads V1 through V3.

1-2-8 Amplitude of initial R decreasing to 2 mm or less in every beat between any of leads V2-V3, V3-V4, V4-V5, V5-V6. Do not code in the presence of 3-2, 7-1-1, 7-2-1, 7-3. All beats in the lead immediately adjacent to the right must have an initial RS >2 mm.

1-3-1 Q/R amplitude ratio at least 1/5 and less than 1/3 plus Q duration of at least 0.02 second and less than 0.03 second in any of leads V2, 3, 4, 5.

1-3-2 QS pattern in absence of code 3-1, in each of leads V1 and V2.

ST Codes (subendocardial ischemia)
ST-Junction (J point) and ST segment depression

(1) Anterolateral ST segment depression (leads I, aVL, V6)

4-1 S-T-J depression 1.0 mm or more and S-T segment horizontal or downward sloping in any of leads I, aVL, V6.

4-2 S-T-J depression at least 0.5 mm and less than 1.0 mm and S-T segment horizontal or downward sloping in any of leads I, aVL, V6.

4-3 No S-T-J depression as much as 0.5 mm but S-T segment downward sloping and segment or T wave nadir at least 0.5 mm below P-R baseline in any of leads I, aVL, V6.

4-4 S-T-J depression of 1.0 mm or more and S-T segment upward sloping or U-shaped in any of leads I, aVL, V6.

(2) Inferior ST segment depression (leads II, III, aVF)

4-1 S-T-J depression 1.0 mm or more and S-T segment horizontal or downward sloping in any of leads II, aVF.

4-2 S-T-J depression at least 0.5 mm and less than 1.0 mm and S-T segment horizontal or downward sloping in any of leads II, aVF.

4-3 No S-T-J depression as much as 0.5 mm, but S-T segment downward sloping and segment or T wave nadir at least 0.5 mm below P-R baseline in lead II.

4-4 S-T-J depression of 1.0 mm or more and S-T segment upward sloping or U-shaped in lead II.

(3) Anteroseptal and anterior ST segment depression

4-1 S-T-J depression 1.0 mm or more and S-T segment horizontal or downward sloping in any of lead V1, 2, 3, 4, 5.

4-2 S-T-J depression at least 0.5 mm and less than 1.0 mm and S-T segment horizontal or downward sloping in any of leads V1, 2, 3, 4, 5.

4-3 No S-T-J depression as much as 0.5 mm, but S-T segment downward sloping and segment or T-wave nadir at least 0.5 mm below P-R baseline in any of leads V2, 3, 4, 5.

4-4 S-T-J depression of 1.0 mm or more and S-T segment upward sloping or U-shaped in any of leads V1, 2, 3, 4, 5.

T Wave Changes (myocardial ischemia)

(1) Anterolateral ischemia (leads I, aVL, V6)

5-1 T amplitude negative, minus 5 mm or more in any of leads I, V6, or in lead aVL when R amplitude is 5 mm or more.

5-2 T amplitude negative or diphasic (positive-negative or negative-positive.type) with negative phase at least minus 1.0 mm but not as deep as minus 5 mm in any of leads I, V6, or lead aVL when R amplitude is 5 mm or more.

5-3 T amplitude zero (flat), or negative, or diphasic (negative-positive type) with less than 1.0 mm negative phase in any of leads I, V6, or in lead aVL when R amplitude is 5 mm or more.

5-4 Optional code: T amplitude positive and T/R amplitude ratio less than 1/20 in any of leads I, aVL, V6; R wave amplitude must be 10 mm or more.

(2) Inferior ischemia (leads II, III, aVF)

5-1 T amplitude negative, minus 5 mm or more in lead II, or in lead aVF when QRS is mainly upright.

5-2 T amplitude negative or diphasic (positive-negative type) with negative phase at least minus 1.0 mm but not as deep as minus 5 mm in lead II, or in lead aVF when QRS is mainly upright.

5-3 T amplitude zero (flat), or negative, or diphasic (negative-positive type) with less than 1.0 mm negative phase in lead II; not coded in lead aVF.

5-4 Optional code: T amplitude positive and T/R amplitude ratio less than 1/20 in lead II; R wave amplitude must be 10 mm or more.

(3) Anteroseptal and anterior ischemia (leads V2, V3, V4, V5)

5-1 T amplitude negative, minus 5 mm or more in any of leads V2, 3, 4, 5.

5-2 T amplitude negative or diphasic (positive-negative type) with negative phase at least minus 1.0 mm but not as deep as minus 5 mm in any of leads V2, 3, 4, 5.

5-3 T amplitude zero (flat), or negative, or diphasic (negative-positive type) with less than 1.0 mm negative phase in any of leads V3, 4, 5.

5-4 Optional code: T amplitude positive and T/R amplitude ratio less than 1/20 in any of leads V3, 4, 5; R wave amplitude must be 10 mm or more.

ST Elevation (injury)

(1) Anterolateral (leads I, aVL, V6)

9-2 S-T elevation 1.0 mm or more in any of leads I, aVL, V6.

(2) Inferior (leads II, III, aVF)

9-2 S-T elevation 1.0 mm or more in any of leads II, III, aVF.

(3) Anteroseptal and anterior (leads V1, V2, V3, V4)

9-2 S-T elevation 2.0 mm or more in any of leads V1, V2, V3, and V4.

ECG EXCLUSIONS

(WPW)

6-4-1 Wolff-Parkinson-White pattern (WPW)--persistent. Normal P wave, P-R interval less than or equal to 0.12 second plus QRS duration 0.12 second or more plus R peak duration 0.06 second or more, consisting in the same beat and present in the majority of beats in any of leads I, II, aVL, V4, 5, 6.

(LBBB)

7-1-1 Complete left bundle branch block (LBBB)--suppressed by 6-1, 6-4, 6-8, 8-2-1 or 8-2-2.

QRS duration $\geq$ 0.12 second in a majority of beats (of the same QRS pattern) in any of leads I, II, III, aVL, aVF PLUS R peak duration $\geq$ 0.06 second in a majority of beats (of the same QRS pattern) in any of leads I, II, aVL, V5, V6. 7-1 suppresses 1-2-3, 1-2-7, 1-2-8, 1-3-2, 1-3-6, all 3, 4, 5, 9-2, 9-4, 9-5 codes.

APPENDIX C

PATIENT EXCLUSION CRITERIA

(for definitions see BHAT
Manual of Procedures)

1. Congestive heart failure within 3 days prior to baseline
2. History of severe congestive heart failure
3. Cardiogenic shock or symptomatic hypotension
4. Pulmonary hypertension with right ventricular failure
5. Mobitz type II, 2:1 AV block or complete AV block within 3 days prior to baseline
6. Heart rate at baseline of less than 50 beats per minute
7. History of frequent or severe intermittent claudication
8. History of bronchial asthma as an adult or chronic obstructive lung disease requiring therapy
9. "Brittle" insulin-dependent diabetes mellitus
10. Patient on MAO-inhibitors, amphetamines and tricylcic antidepressants
11. History of adverse reaction to propranolol or other beta-blocker
12. Women capable of becoming pregnant during the study
13. Wolff-Parkinson-White syndrome
14. Significant angina pectoris since the acute event
15. Hypertension at baseline uncontrolled by therapy ($\geq$ 190 mm Hg systolic or $\geq$ 110 mm Hg diastolic)
16. Other conditions for which the patient is very likely to be placed on propranolol or other beta-blockers before the scheduled termination of the trial
17. Presence of any disease other than the patient's CHD associated with a reduced likelihood of survival for the duration of the trial (e.g. cancer, uremia, liver failure)
18. Patient has undergone or is very likely to undergo cardiac surgery
19. Patient has permanent pacemaker

20. Qualifying myocardial infarction resulted from surgery, trauma, shock or other nonatherosclerotic cause

21. Patient participating in other heart disease trial

22. Patient has been on propranolol or other beta-blocker within 3 days prior to baseline

23. Patient is unwilling or unable (physically or psychologically) to cooperate with the study

24. Patient lives at such a distance from the clinic that travel for follow-up visits would be unusually difficult

25. Patient doesn't anticipate being a resident of the area for the scheduled duration of the trial

26. Patient unwilling to sign consent form

APPENDIX D

GUIDELINES FOR OBTAINING INFORMED CONSENT

The Beta-Blocker Heart Attack Trial will involve patients who are more acutely ill at the time they consent to participate than most subjects in large-scale trials sponsored by the National Heart, Lung, and Blood Institute. The fifth day after their myocardial infarction they will still be very anxious about the possibility of death and prospects for a full recovery. Some will be taking tranquilizing drugs that can interfere with mental alertness, and most will be dependent on medical personnel for help in ambulating, eating, and voiding. Such patients are highly vulnerable to persuasion from health professionals in charge of their care.

Every clinical trial depends for its success on the cooperative participation of its subjects. They must take their medication as prescribed, return for follow-up visits as indicated, and contact their physicians if side effects develop. In the BHAT trial patient cooperation may have added importance because certain data suggest that abrupt termination of the active medication (propranolol) could have deleterious consequences for the patients involved. If our subjects understand this, they may be better compliers than most patients in clinical trials, but if they are confused about the importance of compliance, they may take unnecessary risks.

Various studies suggest that cardiac patients who are recruited into a clinical trial while they are still hospitalized have a higher than average probability of early withdrawal from participation. When heart attack patients return home, the transition can cause unanticipated problems that interfere with involvement in research. Unfortunately, a large number of early withdrawals could seriously reduce the power of our trial to answer crucial questions of interest.

These practical reasons reinforce the ethical imperative that we try to obtain truly informed voluntary consent. If the consent process is simply a mechanical ritual, the trial could be jeopardized not only on ethical grounds, but also by a high number of early drop-outs, poor adherence to therapy, and allegations of coercion.

Basic Elements of Informed Consent

According to DHEW guidelines, informed consent is interpreted to mean:

> "the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion."

The guidelines also set forth seven essential ingredients of informed consent as follows:

1. Patients must be advised of the procedures to be followed and their purposes, including identification of any experimental procedures.

In the BHAT trial none of the procedures is novel or experimental. Propranolol itself has been used for many years to treat patients with high blood pressure and chest pain. However, the drug is not routinely used to prevent recurrent heart attacks or to prolong the lives of infarct patients. The purpose of the BHAT trial is to test its effectiveness in these respects.

We must carefully explain that two kinds of medications (propranolol and a placebo) are being prescribed in the study and that half the patients will be assigned by chance to each therapy group. It is essential that the patient understand that he or she will not necessarily be taking propranolol. It is just as likely that placebo tablets will be prescribed.

Health professionals are not in the habit of discussing with patients the pros and cons of placebo therapy, and there tends to be a feeling among physicians and patients that active treatment with some procedure or drug is always preferable to an inactive approach. Yet, a number of studies have shown that patients may be better off taking an inert placebo than an active medication, if their health status is carefully monitored in both cases.

In our situation we have a special reason for including a placebo group, and patients should be given some understanding of its purpose. This calls for an explanation of the scientific approach to the study--the need to control as many variables as possible. By emphasizing the importance of the placebo group, we explicitly call attention to the fact that this is primarily a study, rather than a therapeutic program specifically designed for the individual. Each patient will be cared for in terms of his or her individual needs, but the scientific design of the study requires that certain conditions must be uniform.

We should carefully explain that this is a double-blind trial in which neither the patient nor the physician will know which medication the patient is taking.

To allay anxiety, it is important to note that not everyone connected with the trial will be "blinded" in the sense of the study. An appropriate person at each medical center will be able to identify the patient's medication in an emergency situation.

Furthermore, a panel of national experts will know which patients are taking which medication and what is happening to each therapy group. If

propranolol proves to be significantly more beneficial than placebo tablets, the study will be stopped so that everyone can have an opportunity to take the drug; and if propranolol proves to be significantly harmful the study will also be stopped, at least for those who might be harmed. Experts who have access to all the data from the trial are in the best position to judge the effectiveness or harm of propranolol for the patients as a whole and special subgroups of them.

With respect to routine procedures, patients should be told that they are expected to take their medication on a daily basis over the course of the trial and have a physical examination every 3 months. To avoid misunderstanding, it should be made clear that the study is expected to last until the summer of 1982.

2. Anticipated benefits of the trial must be explained to patients.

Many patients who have just survived a critical illness appreciate the opportunity to be involved in relevant research and to contribute to medical knowledge. In the BHAT trial the knowledge we gain will be specifically applicable to patients in the study as well as heart attack patients in general, and this is an added benefit of participation.

A number of physicians in this country and abroad are prescribing propranolol for the prevention of recurrent heart attacks without having strong scientific evidence that the drug is effective in this way and that the benefits of long-term use outweigh the risks. It is, therefore, in the patient's interest that a careful scientific study concerned with these issues be conducted as soon as possible.

All patients in the trial will be monitored more closely than the usual heart attack patient, and this could also be advantageous. Furthermore, tests and medications associated with the study are provided at no cost to the patient. The patient will not be charged for propranolol or placebo tablets, periodic examinations relevant to the study, or laboratory tests and electrocardiograms required for the study.

There is no way of knowing in advance whether a particular patient will personally benefit from propranolol during the course of the trial. That will depend on whether the drug is effective and whether the patient is assigned to the propranolol group. We should be careful not to suggest that patients will benefit from propranolol simply by entering the trial. If we were convinced that the drug were effective, we would not be conducting the trial. The study may show that patients on placebo therapy do as well or better than patients on propranolol.

3. Attendant discomforts and risks "reasonably to be expected" must be described.

All drugs have side effects. What is important is their severity and frequency. In the BHAT there is very little likelihood that the subjects will be seriously harmed by participating. To reduce the risk, we have purposely excluded patients for whom propranolol therapy is contraindicated.

In spite of our precautions, however, adverse reactions will still occur. Some patients in the propranolol group (perhaps 5 to 10 percent) will probably experience annoying discomforts from the drug such as sleeping disturbances, fatigue, nausea, and cold feet. If they know such problems can occur, they will be less surprised if they do occur, and we hope they will be less inclined to withdraw from the study.

A few people (perhaps 1 in a 100) may react more severely to propranolol. Their pulse rate or blood pressure may drop precipitously after one or two doses, or they may experience bronchospasm. In other rare instances congestive heart failure or AV block may occur. It should be made clear that patients will be monitored very closely, particularly when they begin taking study medication, so that any problems that arise can be immediately treated. Patients who have an exaggerated response to the medication will be advised not to take it again, and those with heart failure or heart block will either be taken off the study medication or have their dosage reduced, whichever is appropriate.

It is difficult to estimate the exact proportion of patients who are likely to experience adverse effects from propranolol because these effects must be distinguished from problems induced by the natural course of heart disease. We have tried to compare the frequency of problems in propranolol patients and their controls and to base our estimate of side effects on the difference between the two groups.

To avoid the implication that side effects and problems are only linked to the active drug, we should indicate that patients on placebo therapy may also experience discomforts and difficulties similar to those attributable to propranolol. These problems will occur because of the natural history of heart disease and the power of suggestion. Since placebo patients may think they are taking propranolol, they may experience and report more propranolol-related difficulties than otherwise.

We do not wish to frighten patients, but serious events are within the realm of possibility and should be so described.

In the course of the consent discussion, patients should be told that the abrupt termination of propranolol may also cause problems such as chest pain. Since no one will know what medication he or she is taking, it is probably safest for patients to assume that they are in the treatment group.

4. Appropriate alternative procedures that might be advantageous for the subject must be disclosed.

This mandate is often overlooked in written consent forms. It means that the patient should be told what options exist if he or she elects not to participate in the trial. In our situation patients have the alternative of being treated for heart disease without being involved in the BHAT study at all. They also have the option of being treated with

propranolol if their physician decides such a therapeutic approach is appropriate.

Patients who are taking beta-blocking drugs in the hospital or are likely to need them during the course of the trial are ineligible for enrollment. If they join the trial and then develop a condition for which a beta-blocker is the most appropriate therapy, their physicians will be advised to terminate the study medication (whatever it is) and prescribe the drug they wish. Where there is uncertainty regarding the best therapy for the patient's condition, it is recommended that drugs other than beta-blockers be tried first.

According to the protocol for the trial, beta-blocking drugs are the only medications that cannot be taken in conjunction with the study medication (propranolol or placebo tablets). However, it is suggested that physicians use caution in prescribing amphetamines or MAO-inhibitors for patients participating in the trial.

5. Persons responsible for the study must offer to answer any inquiries concerning procedures.

We suggest that one or more people associated with the trial be available to answer relevant questions while patients are contemplating participation. Prospective subjects should be handed the names of these people on a card when they are first approached. If no names are provided, they may ask questions of persons unknowledgeable about the study and be given evasive answers or misinformation.

6. Patients must be told that they can withdraw from the trial at any time without prejudicing their future care.

We obviously would like our subjects to remain in the study as long as possible, but they have the right to withdraw at any time. We must communicate this option to patients without luring them into the trial on a probationary "look and see" basis. Hesitant patients should be evaluated very carefully to screen out those who are likely to withdraw early.

The right to withdraw from a trial is meaningless if such behavior invokes penalties. This is the reason for the phrase "without prejudice," and that idea should be explained to patients. If they drop out of the trial, the fact of dropping out will not jeopardize their regular care, and we will welcome them back to the study at any time they wish to return.

7. Prospective subjects must be advised of the availability or non-availability of medical treatment or compensation for physical injuries incurred as a result of participation in the study.

It may be useful to distinguish between financial reimbursement for actual treatment costs and other types of financial compensation for

injuries incurred. The Federal Government is prohibited by law from commiting funds that have not yet been appropriated by Congress, and no funds have been allocated for compensating injured subjects in trials such as BHAT. The only recourse for such patients is to seek compensation through the courts or through negotiation with the clinical center involved.

Reimbursing the cost of medical treatment for a research-induced injury is a separate issue. Every effort will be made by the project office and the cooperating centers to reimburse injured subjects for their medical expenses if the patients are required to pay such costs out of their own pockets. Any such problems will be dealt with on a case by case basis.

Policies regarding compensation and reimbursement vary from institution to institution, so we cannot recommend a standard approach for all participating centers. However, on the basis of our observations to date, we offer several suggestions. Staff members should stress the fact that the chance of serious injury in BHAT is extremely small but the government requires that compensation be discussed with patients if there is any risk at all. Legal terms and concepts should be translated into layman's language, and the ideas should be made relevant to BHAT, not simply to research in general. Comments regarding compensation should be as brief as possible. Where every contingency is described, these statements tend to be lengthy and out of balance with the rest of the consent form. They give the impression that injuries are likely to occur, even though we say elsewhere that the probability of serious side effects from propranolol is less than 1 percent.

The Process of Obtaining Consent

The seven ingredients of informed consent in the DHHS guidelines refer primarily to categories of information that enable patients to make rational decisions regarding participation in clinical trials. Except for the stipulation that patient inquiries should be answered, these basic elements do not refer to the process of obtaining informed consent.

Various studies indicate that the circumstances under which consent is obtained in clinical trials can have a profound influence on the patient's interpretation of information communicated during the consent discussion and on the freedom of patients to make their own decisions.

Given the data at hand, we are recommending the following guidelines to ensure that the consent we obtain will be as informed and voluntary as possible:

1. In approaching a patient to discuss the propranolol study, the person responsible for making the initial contact should try to determine when that patient is likely to be most alert and comfortable.

Ideally, patients should be out of the CCU when they are first approached so they can discuss the study in a more relaxed environment. If time considerations make this impossible, extra care should be taken to respect the patient's need for sleep, rest, privacy, and family companionship.

2. Patients should have adequate time to evaluate the pros and cons of participation.

In the BHAT trial we suggest that a period of at least 24 hours should elapse between the time the patient is first contacted about the study and the time informed consent is obtained. If the logistics of hospital confinement necessitate a quicker response, patients should be asked how much time they need to make a thoughtful decision, and their request should be respected. We are asking patients to commit their time and effort to the study over the next several years, and that commitment should not be taken lightly.

3. Patients should be encouraged to discuss the study with anyone they wish, particularly family and friends who might be affected (for example, persons who might be needed to provide transportation).

Close associates of the patient may raise questions and considerations that the patient is likely to overlook because of more immediate problems, and questions that concern the family are better answered sooner than later. Furthermore, there is evidence to suggest that family support for studies of this kind increases the probability of patient cooperation during the course of the research.

4. To be eligible for participation in the BHAT trial patients must have the capacity to give their <u>own</u> informed consent.

If a patient is incapable of understanding what is expected of him or her as a subject in the study, it is not permissible to obtain informed consent from a guardian. The study requires daily responsibilities that cannot be easily assumed by other persons.

5. Before the patient's consent is obtained, the principal investigator or coinvestigator should make certain the patient has been fully informed about the study.

If the investigator is not involved in the consent process, he or she should thoroughly question intermediaries regarding the patient's comprehension of the trial. In this way, persons responsible for obtaining consent will appreciate the importance of the "informed" aspect of the consent process.

6. The setting in which consent is obtained (i.e. where the patient reads the consent form and signs it) should resemble as much as possible the patient's natural decision-making world.

Obviously, patients will still be in the hospital when they consent to participate in our study, but they should at least be out of the CCU or off "hard wire" if they are required to remain in a CCU until discharge. Where they are ambulatory, patients should select the environment in which they feel most comfortable--a lounge, a nearby examining room, or their bed.

7. The setting in which consent is obtained should be as private as possible so patients can freely ask questions without embarrassment. If extraneous parties can hear the conversation, patients may be reluctant to ask appropriate questions.

8. To avoid pressuring the patient, only one person associated with the study should be present when the patient reviews the consent form.

If the hospital requires the presence of an ombudsman or patient advocate, that person would not be considered a representative of the study. If a second witness is required, he or she should be as unobtrusive and noncommital as the situation permits.

9. The patient should be given a copy of the informed consent form after it is signed and witnessed.

Even though patients are free to withdraw from the study at any time, the consent form spells out our obligations to the patient and the patient's obligations to the study while he or she is a subject.

10. Patients should be encouraged to keep the consent form because it contains useful information about the study which they can review from time to time.

Reducing the Vulnerability of Patients

The DHHS guidelines stress the importance of voluntary consent in clinical trials. One hospital in the BHAT trial is requiring that the person responsible for obtaining the patient's consent be someone who is not associated with that patient's care. The institutional review board for this hospital is concerned that patients who have recently had a myocardial infarction are highly vulnerable to persuasion from professionals involved in their care. We recognize this problem, but we are not suggesting that the principal investigators in the BHAT trial be divorced from the consent process, even if their own patients are candidates for inclusion in the study.

We do, however, wish to emphasize that a patient's trust in his or her physician is not a substitute for truly informed voluntary consent. Where dependency is particularly evident, we must be especially careful to give patients all the freedom they need to say "no" if this is their inclination.

Where the person responsible for obtaining the patient's consent is also the person in charge of that patient's care, patients must be told in no uncertain terms that they will be treated with the same degree of interest and concern regardless of whether they participate in the study.

In approaching the issue of informed consent, we should keep in mind its two essential components--information and voluntary choice. When we share with patients important facts about the BHAT trial, we treat them as potential partners in our research and enable them to rationally evaluate their capacity and willingness to participate. By fully disclosing information about the study, we are expressing respect for our patients and reducing their vulnerability to coercions.

REFERENCES

The issue of informed consent in medical research is currently attracting a great deal of interest. The following references seem particularly relevant and can probably be obtained in your medical library:

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APPENDIX E

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